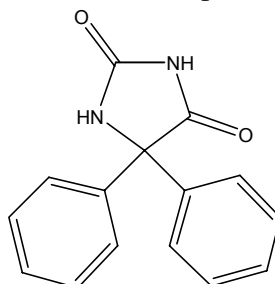


**PHENYTOIN**  
**CAS No. 57-41-0**

First Listed in the *First Annual Report on Carcinogens*



## CARCINOGENICITY

Phenytoin is *reasonably anticipated to be a human carcinogen* based on limited evidence of carcinogenicity in humans. An IARC Working Group reported that there is limited evidence for the carcinogenicity of phenytoin in humans (IARC S.1, 1979; IARC S.4, 1982; IARC S.7, 1987). Cancer, mostly neuroblastoma and tumors of neural crest origin, has been reported in six children aged 3 years or less who had been diagnosed as having congenital abnormalities thought to be induced by prenatal exposure to phenytoin. Although the number of patients is small, the concordance of rare events suggests that phenytoin may be a transplacental carcinogen in humans. There is also one report of malignant mesenchymoma in a patient with phenytoin malformations (IARC S.4, 1982). There have been several case reports of lymphomas among individuals under phenytoin therapy. However, no significant excess of lymphoma was reported in two follow-up studies of epilepsy patients. An increased incidence of brain and other neurological tumors was reported among people prescribed phenytoin. This incidence is similar to that reported among epileptics and may reflect the underlying disease rather than use of the drug per se (IARC V.13, 1977; IARC S.1, 1979; IARC S.4, 1982). Based on evidence compiled by the Epilepsy Branch of NINCDS, NIH and FDA did not find the data clear-cut or adequate to support a conclusion of carcinogenicity of phenytoin in humans (Scoville & White, 1981).

There is limited evidence for the carcinogenicity of phenytoin in experimental animals (IARC S.1, 1979; IARC S.4, 1982; IARC S.7, 1987). When administered in the diet, phenytoin induced increased incidences of thymic and generalized lymphomas in female mice. Intraperitoneal injection induced increased incidences of thymic and mesenteric lymphomas and leukemias in mice of both sexes (IARC V.13, 1977).

## PROPERTIES

Phenytoin is a white crystalline powder that is practically insoluble in water and benzene, but soluble in ethanol, acetone, acetic acid and alkali hydroxides. When heated to decomposition, it emits toxic fumes of nitrogen oxides (NO<sub>x</sub>). Phenytoin is available in the United States as a grade containing 98.5%-100.5% active ingredient on a dried basis. When heated to decomposition, it emits toxic fumes of carbon monoxide, carbon dioxide, and nitrogen oxides.

## **USE**

Phenytoin is an anticonvulsant drug used alone, or in combination, with phenobarbital or other anticonvulsants to treat grand mal epileptic patients with focal and psychomotor seizures. Phenytoin can also be used to control seizures occurring during neurosurgery, to reverse digitalis-induced arrhythmias (particularly ventricular arrhythmias), and to prevent postcountershock arrhythmias in digitalized patients (Kirk-Othmer V.4, 1978; Kirk-Othmer V.13, 1981). Phenytoin has been used in the treatment of chorea or Parkinson's syndrome to control involuntary movements. It has been investigated for the treatment of trigeminal neuralgia, migraine, polyneuritis of pregnancy, acute alcoholism, and certain psychoses, but these uses have not been approved by FDA. Phenytoin is also used to control epileptic-like convulsions in dogs (IARC V.13, 1977).

## **PRODUCTION**

The USITC identified one manufacturer of phenytoin and sodium phenytoin from 1980 to 1986, but no production volumes were reported (USITC, 1987). The 1984 Chem Sources USA directory identified two producers and one supplier of phenytoin (Chem Sources, 1984). In 1983, U.S. imports of phenytoin were 551 lb, and imports of its sodium salt were close to 15,000 lb (USITCa, 1984). The 1979 TSCA Inventory identified one company producing phenytoin sodium (no volume reported) and two companies importing 500 lb in 1977, with some site limitations; phenytoin itself was not reported in the inventory (TSCA, 1979). In 1977, total estimated U.S. sales of phenytoin for use in human medicine were less than 172,000 lb annually. In 1974, imports exceeded 5,000 lb. Commercial production of phenytoin was first reported in the U.S. in 1946 (IARC V.13, 1977). Sales in the U.S. for 1990 were 1,093,290 standard dosage units. Sales in the U.S. for 1995 was 984,527 standard dosage units (HSDB, 1997)

## **EXPOSURE**

The primary routes of potential human exposure to phenytoin are injection, ingestion, inhalation, and dermal contact. Statistics on the number of patients using phenytoin are not available, but the drug is given to a major segment of individuals suffering from epilepsy. The oral dosage for adults and children over 6 years of age is initially 100 mg 3 times per day; the dosage may be gradually increased by 100 mg every 2-4 weeks until the desired therapeutic response is obtained. Maintenance dosages usually range from 300-600 mg daily for adults, and 3-10 mg/kg body weight daily for children under 6 years of age. As a cardiac depressant, phenytoin is usually administered in an oral dose of 100 mg 2-4 times per day. Sodium phenytoin is usually administered by intravenous or intramuscular injection (IARC V.13, 1977). Potential exposure of health professionals may occur during the preparation and administration of the compound. Potential occupational exposure may also occur for workers involved in the formulation and packaging of the pharmaceuticals. Since phenytoin and its sodium salt are produced by a single domestic manufacturer, occupational exposure may be site-limited.

## **REGULATIONS**

Phenytoin is an anticonvulsant drug used as a pharmaceutical in relatively small quantities, therefore EPA has minimal regulatory interest in phenytoin and its monosodium salt. EPA has no indication of their presence in effluents, emissions, or wastes from pharmaceutical manufacturers. However, the monosodium salt of phenytoin was reported in the TSCA

Inventory, which indicates that there may be other uses. The small production volume, compared with other chemicals (including carcinogens) of concern, may limit interest for the foreseeable future. FDA regulates phenytoin as a prescription drug approved for human use. FDA's Center for Drugs and Biologics is examining the information on potential human hazards from phenytoin, and an advisory committee will recommend further regulatory action if required. OSHA regulates phenytoin under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table B-121.